



CASE MANAGEMENT RESEARCH PRIORITIES

The primary objective of the Programme for the Control of Acute Respiratory Infections is to reduce deaths from these infections in children under 5 years of age. Most of the deaths are due to pneumonia. The central control strategy to reduce these deaths is correct case management. The case management strategy aims to reduce mortality by making antibiotic therapy for pneumonia available to children and ensuring that the therapy is used properly. The technical bases of this strategy need to be strengthened in several areas.

1. Pneumonia in children age 2 months up to 5 years

1.1 Background

The clinical assessment is crucial for correct case management. Its main purpose is to decide whether a child should receive empirical antibiotic therapy at home or be referred for hospital care (including parenteral antibiotics). For simplicity and ease of training, a small number of criteria that can be reliably taught and are adequate for each decision about management have been identified.

The current protocol (summarized on the ARI case management chart "Management of the child with cough or difficult breathing" is based on available evidence from research studies and the best expert advice. The protocol has given a satisfactory performance in studies conducted in two settings (Philippines and Swaziland) in children age 2 months up to 5 years. Further studies are needed to evaluate it more fully and define the best clinical signs for predicting severe pneumonia or very severe disease that would benefit from hospital care. The clinical signs and symptoms indicating pneumonia and very severe disease are even less well known in the young infant (age less than 2 months) (see section 2).

1.2 Priority research questions/objectives

- 1.2.1 Identify the signs or symptoms that best identify children with severe pneumonia (and very severe disease) who are at higher risk of death and would benefit from hospital care (parenteral antibiotics, oxygen, greater clinical expertise, and more nursing care).
- 1.2.2 Assess the prevalence of significant hypoxaemia amongst children with pneumonia.
- 1.2.3 Evaluate the performance of the ARI protocol, including the management of children with wheezing, at first-level facilities (see section 5).
- 1.2.4 Compare the clinical presentation of pneumonia and malaria.
- 1.2.5 Identify ways of defining and teaching the clinical signs and symptoms that will ensure reliable observation by different categories of health workers.

If their results are to be relevant to clinical practice, these studies should not only assess the diagnostic sensitivity, specificity, and predictive value of clinical signs, symptoms, and various historical factors (including maternal perception of sickness) but should also assess the efficiency of case detection of pneumonia. Careful assessment for possible pneumonia is time-consuming because of the need to calm the child and the time required to obtain an adequate respiratory rate measurement. Thus the

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minimum number of "entry" criteria that is consistent with adequate sensitivity in detecting pneumonia cases should be identified. The studies must minimize the verification bias common to most studies, whereby the standard for diagnosis of pneumonia (chest X-ray) is applied only to cases with the clinical signs being evaluated. A sample of children without these clinical signs should also be X-rayed.

To ensure that the results are as relevant as possible to health care delivery at first-level facilities, it is important to distinguish presenting symptoms according to whether they are (i) volunteered by the mother and constitute a chief complaint; (ii) admitted to by the mother on questioning; and (iii) observed by the health worker on clinical examination. This has relevance for constructing and teaching case management protocols.

Ideally, a case definition of severe disease should be related to the care that can be provided at the small hospital. The study results should demonstrate or at least infer that a referral based on criteria of severe disease will lead to a better disease outcome as a result of the available referral care. Referral of children who are most likely to die is not the goal (death in hospital is not intrinsically desirable). The aim should be to refer children at high risk of death whose death would be averted by referral care. Such information will help programmes to estimate what can reasonably be expected in terms of mortality reduction from making hospital care more widely available.

Children assessed by a health worker have already been judged to be sick by their mother. This is important information, and its usefulness to the health worker in making his/her evaluation should be studied. Ethnographic work is in progress to help define the relationship between signs recognized by the mother and clinical pneumonia¹. In clinical studies, several questions should be asked of the mother to allow the investigator to evaluate the significance of her perception that the child is sick and determine the relationship of the signs she recognizes to clinical and radiographic pneumonia.

The studies should also assess the best ways of eliciting certain signs and symptoms to improve test performance. They should try to identify practical ways of improving the specificity of certain clinical signs in the case detection of pneumonia (for example, can false positives be reduced by repeating the respiratory rate measurement when it is elevated or by clearing any nasal obstruction if chest indrawing is observed?).

2. Pneumonia (and sepsis and meningitis) in young infants (age less than 2 months)

2.1 Background

Among children in developing countries, pneumonia occurs with greatest severity and fatality in young infants. Of the deaths attributed to ARI in children age less than 5 years, 20-30% occur in the first two months of life in most developing countries. Despite this fact, little is known about the etiology of pneumonia, meningitis, or sepsis in this age group, the performance of clinical signs and symptoms in the diagnosis of these infections, and their clinical outcome. There is a need for carefully performed studies of acutely ill young infants in several developing countries, using standardized clinical and laboratory evaluations (chest X-rays, pulse oximetry, blood cultures, lumbar punctures, and other diagnostic evaluations), in order to improve the recommendations for case management and prevention.

¹ Behavioural research priorities. Document WHO/ARI/RES 90.2.

The WHO/ARI case management protocol for young infants differs from that used for older children for several reasons. The main one is that pneumonia can present with only non-specific clinical signs which overlap with those of meningitis and sepsis; thus case detection and rapid antibiotic treatment must be directed at this broader category of serious bacterial infection. Also, the efficacy of home antibiotic treatment has not been established for young infants with pneumonia or another serious bacterial infection; thus WHO recommends hospital referral of these cases and parenteral treatment with benzylpenicillin and gentamicin. The Programme has relied on expert opinion and data from a small number of clinical studies to assemble a list of clinical signs and symptoms for the detection of cases of pneumonia, sepsis, or meningitis in young infants (see the ARI case management chart "Management of the child with cough or difficult breathing").

At present, the entry criteria that indicate which young infants should be examined for possible pneumonia are the same as those for older infants and children. The adequacy of these criteria for young infants has not been formally studied.

Although the WHO/ARI case management guidelines recommend that young infants with pneumonia, sepsis, or meningitis be referred to hospital for treatment with parenteral benzylpenicillin and gentamicin, this is not possible in many rural settings, leaving oral cotrimoxazole as the only treatment option. However, there is little information on the use and efficacy of cotrimoxazole in the first two months of life.

2.2 Priority research questions/objectives

2.2.1 In young infants (age less than 3 months) brought for illness to a health facility:

- (a) Determine the sensitivity, specificity, and predictive value of initial signs, symptoms, and historical factors (alone and in combination) in the diagnosis of serious bacterial infection (pneumonia, sepsis, and meningitis), with the aim of defining specific clinical features (or combinations of features) that would facilitate early recognition of these infections by health workers;
- (b) Determine the relative prevalence of pneumonia, sepsis, and meningitis cases among sick infants in this age group;
- (c) Assess the prevalence of positive bacterial cultures of Haemophilus influenzae, Streptococcus pneumoniae, gram negative organisms, group B streptococcus, and Staphylococcus aureus using standard blood and cerebrospinal fluid culture techniques, and characterize the isolated bacteria, including their antimicrobial sensitivity;
- (d) Assess the prevalence of significant hypoxaemia;
- (e) Identify the etiology and characterize the clinical features of other potentially important causes of pneumonia in young infants (such as respiratory viruses, Chlamydia trachomatis, Pneumocystis carinii, and Bordetella pertussis); and
- (f) Determine the relationship between selected risk factors (which can be ascertained during the clinic visit) and the outcome in infants with pneumonia, other respiratory diseases, sepsis, and meningitis.

- 2.2.3 Determine the optimal antibiotic treatment regimens for pneumonia, sepsis, and meningitis in young infants.
- 2.2.4 Determine the pharmacokinetics and toxicity of oral cotrimoxazole in young infants with pneumonia or another serious bacterial infection.

A protocol for a multicentre study of the clinical signs and etiological agents of pneumonia, sepsis, and meningitis in young infants was prepared at a meeting attended by advisers and investigators from five study sites that are considered to have the potential and interest to carry out a technically demanding study in infants age less than 3 months².

In the multicentre study, hospitalized infants at several locations will also be enrolled in a treatment study to compare intramuscular chloramphenicol or oral cotrimoxazole with the current standard regimen - benzylpenicillin and gentamicin. An initial evaluation of the pharmacokinetics of these alternative regimens in young infants will be carried out before the treatment studies start.

3. Pneumonia in severely undernourished children

3.1 Background

Undernourished children often come for medical attention because of respiratory infections. Severely undernourished children frequently die from bacterial infections and there is evidence that they are more prone to pneumonia than well-nourished children.

Hospital-based studies suggest that undernourished children who have bacteraemia are, in comparison with their well-nourished counterparts, less likely to be infected with H. influenzae and S. pneumoniae but more likely to be infected with gram negative organisms like Pseudomonas spp., Klebsiella, and Escherichia coli. There is some evidence that undernourished children are susceptible to tuberculosis and opportunistic infections such as those caused by P. carinii and Cryptosporidium.

Severely undernourished children may have a weak or absent cough. The clinical signs used in the ARI case management protocol, tachypnoea and chest indrawing, are functions of increased respiratory labour in response to parenchymal lung impairment causing decreased compliance and hypoxia. There is a suspicion that severely undernourished children may not manifest these physical signs and this needs to be investigated further.

The pharmacodynamics of chloramphenicol in undernourished children is complex and poorly understood. One study of oral chloramphenicol showed that, compared with normal children, undernourished children achieved peak levels later (4-6 hours compared with 2 hours) but the peaks were higher and the half-life longer. However, another study showed a shorter half-life. Since the liver is responsible for converting chloramphenicol succinate into free chloramphenicol and liver function is impaired while renal function is relatively well preserved in undernutrition, it is possible that blood levels following parenteral administration may actually be low in undernourished children. Further study is needed to resolve these questions and determine the optimal mode of administration and dose of chloramphenicol in undernourished children.

3.2 Priority research questions/objectives

- 3.2.1 Determine the sensitivity and specificity of clinical signs and symptoms as predictors of pneumonia in a population of undernourished children, in comparison with the performance of the same signs as predictors of pneumonia in well-nourished children.

² Clinical signs and etiological agents of pneumonia, sepsis, and meningitis in young infants. Report of a meeting. Document WHO/ART/90.14.

- 3.2.2 Investigate the etiology of pneumonia in undernourished children and determine whether it differs from the etiology in well-nourished children.
- 3.2.3 Determine the pharmacokinetics of oral and intramuscular chloramphenicol in undernourished children.

4. Oxygen administration

4.1 Background

Some children with very severe pneumonia or other severe lower respiratory infections (e.g., bronchiolitis) may require oxygen therapy in addition to antibiotic treatment if they are to survive. Unfortunately, in many developing countries, oxygen is unavailable or in short supply. For these reasons, oxygen delivery must be efficient as well as safe and effective. Two delivery systems have been proposed: the nasal catheter (a thin tube inserted into the nasopharynx) and the nasal cannula (a tube that crosses the cheek and has two short outlet barrels which direct the flow into the nostrils).

4.2 Priority research questions/objectives

- 4.2.1 Compare the oxygen flow rate required to achieve adequate oxygenation using a nasal catheter and nasal cannula, and the safety and rate of complications experienced with each method.

5. Wheezing

5.1 Background

Overall, wheezing studies have only moderate priority within the ARI Programme. The technical guidelines for the management of wheezing in first-level facilities and small hospitals in developing countries are based on expert advice and limited data from such countries. These recommendations need to be very vigorously evaluated. Although improved management of wheezing will not substantially affect mortality, the condition cannot always be ignored. Children with wheezing conditions present with cough or difficult breathing, and some children with bacterial pneumonia wheeze.

5.2 Priority research questions/objectives

- 5.2.1 Develop a scoring system to allow reproducible assessment of the severity of wheezing in young children.

In general, in the under-5 age group, there is no objective measure of airway obstruction. Oximetry and blood gas analysis provide evidence of severity in the few children in whom these investigations are abnormal, but are not useful in the majority. This leaves the doctor's clinical judgment as the main "gold standard". This is problematic since the performance of individual clinical signs, such as respiratory rate, must be compared with the doctor's judgment, to which these clinical signs will probably have contributed. Oxygen saturation, pulmonary function tests (in older children), and an internal standard will be used to construct a functional score. The score would be used in the studies described below.

- 5.2.2 In infants and children age 1-4 years, compare the efficacy of various methods of administering bronchodilators that are feasible in first-level facilities and small hospitals in developing countries, including subcutaneous epinephrine, salbutamol by foot-pump nebulizer, salbutamol by metered-dose inhaler with a spacer device, and salbutamol delivered by an electric nebulizer.

5.2.3 Evaluate the performance of the ARI protocol in assessing and treating children with wheezing. Can first-level facility workers be trained to recognize wheezing and correctly assess response to bronchodilator therapy (without the use of a stethoscope)?

5.2.4 In the course of studies on clinical signs of pneumonia and other acute lower respiratory infections:

(a) Determine the clinical signs of hypoxia in bronchiolitis and asthma; and

(b) Determine how often children presenting with a first episode of wheezing or with recurrent wheezing have bacterial pneumonia (by age).

6. Standards for studies

Standardized observations of clinical signs are necessary to allow comparison of the results of studies.

During 1989 a standardized list of definitions of clinical signs was developed for future use. A meeting of radiologists was held in October 1989 to establish a standardized methodology for the scoring of paediatric chest X-rays. Studies were initiated to assess the degree of inter-observer variability amongst the group and the extent to which the taking of a lateral chest X-ray results in an altered or more certain diagnosis. This group will review all chest X-rays from studies supported by the Programme during the next four years.

Methods to help standardize clinical observation during research studies, using audio tapes, videos, and other learning aids, are being developed. Intra- and inter-observer variability in the observation of signs will be assessed.

7. Other case management research priorities

The efficacy of cotrimoxazole as an antimalarial is currently under study. The evaluation of simplified and shortened antibiotic schedules for home treatment of pneumonia requires a multicentre study to achieve an adequate sample size. This will be pursued later when staff and funding permit.

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